ajamaline, amylobarbitone, bendrofluazide, benzonatate, benzylbenzoate, betamethazone, chloramphenicol, chlorpropamide, chlorthalidone, clofibrate, corticosteroids, diazepam, dicumerol, digitoxin, dihydroxypropyltheophylline, ergot alkaloids, ethotoin, frusemide, glutethimide, griseofulvin, hydrochlorothiazide, hydrocortisone, hydroflumethiazide, hydroquinone, hydroxyalkylxanthines, indomethacin, isoxsuprine hydrochloride, ketoprofen, khellin, meprobamate, nabilone, nicotainamide, nifedipine, nitrofurantoin, novalgin, nystatin, papaverine, paracetamol, phenylbutazone, phenobarbitone, prednisolone, prednisone, primadone, reserpine, romglizone, salicylic acid, spiranolactone, sulphabenzamide, sulphadiamadine, sulphamethoxazole, sulphathiazole, sulphisoxazole, testosterone, tolazoline, tolbutamide, trifluoperazine, trimethaprim, and mixtures thereof.

REMARKS

Brief Summary of the Present Invention

In the Office Action, claims 1-7 were rejected. In the present Amendment, claims 1 and 3 have been amended and claims 8-20 have been added. Thus, claims 1-20 are pending. The amendments to the existing claims are supported in the specification and, thus, no new matter is added.

Rejections Under 35 U.S.C. § 102(b)

Claims 1-3 and 7 were rejected under 35 U.S.C. § 102(b) as anticipated by JP-5-4919 ('919) or WO 93/11749 ('749). The applicant traverses the rejection for the reasons set forth below.

The Office Action alleged that '919 and '749 teach troglitazone in a solid dispersion comprising polyvinylpyrrolidone (PVP). The applicant submits that '919 teaches solid dispersions containing thiazolidines and PVP dissolved in acetone and ethanol. Claim 1 of the instant application discloses a sparingly water-soluble pharmaceutical agent in crystalline particulate form, wherein said particulate is at least partially coated with a solidified matrix comprising a water-soluble polymer. The specification discloses, on page 5, lines 19-22, that the solid

particulate dosage form is prepared without the use of aqueous or organic solvents. It is well known in the art that the use of organic and aqueous solvents in the preparation of solid pharmaceutical dispersions is lengthy, costly, and potentially hazardous. Further, there is no indication in '919 that the thiazolidines are in crystalline form or coated with a solidified water-soluble polymer, nor would one expect the products of '919 to be in this form based on the method of their preparation. The applicant asserts the instant invention as claimed by amended Claim 1 is not anticipated by '919. Accordingly, withdrawal of the rejection is respectfully requested.

The applicant submit that '749 teaches a solid pharmaceutical dispersion combining a poorly water-soluble drug with a polymer carrier such as PVP and a transition compound which partially solubilizes the drug and/or plasticizes the polymer. As indicated above, claim 1 of the instant application discloses a sparingly water-soluble pharmaceutical, crystalline particulate partially coated with a solidified matrix comprising a water-soluble polymer. Nowhere does '749 disclose retaining the form of the pharmaceutical agent as crystalline. The inventor of the present application, also an inventor of '749, has informed the undersigned that such a process was not contemplated in the invention that led to '749. '749 does not anticipate the claims of the instant invention. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 1-3 and 6 were rejected under 35 U.S.C. § 102(b) as anticipated by WO 95/32713 ('713). The applicant traverses the rejection for the reasons set forth below.

The Office Action alleged that '713 teaches troglitazone in a solid dispersion comprising hydroxypropyl methylcellulose (HPMC). The applicant submits that '713 teaches a solid dispersion comprising a thiazolidine derivative, a water-soluble polymer other than HPMC or methylcellulose (MC), **and** HPMC and/or MC. Similar to '919, '713 teaches first dissolving a thiazolidine derivative in PVP, then removing the solvent before mixing with the other constituents. This method of preparation does not result in a pharmaceutical agent in crystalline

particulate form, wherein said particulate is at least partially coated with a solidified matrix comprising a water-soluble polymer, as called for by Claim 1. Therefore, the claims of the instant application are not anticipated by '713. Accordingly, withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-7 were rejected under 35 U.S.C. § 103(a) as unpatentable over Olefsky *et al.* (U.S. Patent No. 5,478,852) in view of Grabowski *et al.* (U.S. Patent No. 5,641,516). The applicant traverses the rejection for the reasons set forth below.

The Office Action alleged that Olefsky *et al.* teach troglitazone and rosiglitazone and Grabowski *et al.* teach "delayed release compositions which are solid compositions comprising an active and a polymer." Further, the Office Action alleged, "It would have been obvious to one of ordinary skill to deliver the compounds of Olefsky *et al.* with the vehicle of Grabowski *et al.* to achieve the beneficial effect of delayed release." Olefsky *et al.* disclose a method of treatment using troglitazone in a pharmaceutically acceptable carrier. Grabowski *et al.* teach a solid composition comprising an active substance with a polymeric melt of a water-soluble polymer A, such as MC, HPC, and/or HPMC, and a water-soluble polymer B, such as HPC, PVP, and/or vinyl pyrrolidone/vinyl acetate copolymers.

The applicant asserts that amended claim 1 of the instant invention discloses a pharmaceutical agent in crystalline particulate form, wherein the particulate is at least partially coated with solidified water-soluble polymer. Claim 1 does not disclose the use of two or more water-soluble polymers with the pharmaceutical particulate. Further, Grabowski *et al.* disclose, at column 3, lines 3-9, that "the particular active substance can be present in the compositions according to the invention in ***amorphous*** form, virtually homogeneously dispersed in the melt." (Emphasis added) This is known in the art as a molecular dispersion. The pharmaceutical agent of the instant invention is in ***crystalline*** form, which is more stable than pharmaceutical agents in amorphous form in molecular dispersions

and solutions. In addition, the process of Grabowski *et al.* describes a "one-step" method of mixing, extruding, and compressing the composition directly into tablet form. The process of the instant invention further comprises the steps of milling the extrudate, blending with at least one additional excipient, and then compressing or encapsulating into tablet or capsule form. This unique process allows for the use of higher concentrations of the pharmaceutical agent in the blending and extruding steps.

In view of the foregoing, the applicant strongly asserts that neither Olefsky *et al.* nor Grabowski *et al.* discloses the instant invention. Likewise, combining the compound of Olefsky with the vehicle of Grabowski would not produce the solid particulate dosage form of the instant invention. Therefore, the instant invention is patentable over Olefsky *et al.* in view of Grabowski *et al.* Accordingly, withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112(2)

Claims 1-7 were rejected under 35 U.S.C. § ***112,*** second paragraph, as indefinite for failing to particularly point out and distinct claim the subject matter regarded as the invention. Specifically, the Office Action alleged that the recitation of the term "sparingly" in claim 1 is vague. The applicant traverses the rejection for the reasons set forth below.

The applicant is submitting with this Amendment the United States Pharmacopoeia (USP) definition of solubility. The USP definition of "sparingly" soluble is 30 to 100 parts of solvent required for 1 part solute at 25°C. This definition is also disclosed in the specification, on page 3, lines 26-29. The applicant asserts that the term "sparingly" water-soluble is well known in the art and therefore a skilled artisan would both recognize and understand the term. Therefore, the term "sparingly" water-soluble is not vague or indefinite. Accordingly, withdrawal of the rejection is respectfully requested.

Summary

In view of the foregoing amendments and remarks, the applicant submits that this application is in condition for allowance and respectfully request early and favorable notification to that effect. If it would expedite prosecution of this application, the Examiner is invited to confer with the applicant's undersigned attorney.

Respectfully Submitted,

RATNER & PRESTIA

Christopher R. Lewis, Reg. No. 36,201
Attorney for Applicant

CJT/fp/lrb

Dated: October 17, 2000

Suite 301
One Westlakes, Berwyn
P.O. Box 980
Valley Forge, PA 19482-0980
(610) 407-0700

The Assistant Commissioner for Patents is hereby authorized to charge payment to Deposit Account No. 19-2387 of any fees associated with this communication.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on:

October 17, 2000

Christopher R. Lewis